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International filing date (day/month/year) 07 August 1999 (07.08.99)	**Priority date** (day/month/year) 12 August 1998 (12.08.98)
Applicant DIETRICH, Rango et al	

1. The designated Office is hereby notified of its election made:

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10 February 2000 (10.02.00)

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2. The election [X] was

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(71) Applicant *(for all designated States except US)*: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH [DE/DE]; Byk–Gulden–Strasse 2, D–78467 Konstanz (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: DIETRICH, Rango [DE/DE]; Im Tiergarten 16, D–78465 Konstanz (DE). NEY, Hartmut [DE/DE]; Peter–Thumb–Strasse 46, D–78464 Konstanz (DE).

(74) Common Representative: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; Byk–Gulden–Strasse 2, D–78467 Konstanz (DE).

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(57) Abstract

The invention relates to an oral administration form for pyridin–2–ylmethylsulfinyl–1H–benzimidazoles and their salts, which comprises the active compound together with tablet disintegrants and is provided with a film coating customary per se for sustained–release compositions.

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ORAL ADMINISTRATION FORM FOR PYRIDIN-2-YLMETHYLSULFINYL-1H-BENZIMIDAZOLES

Subject of the invention

The present invention relates to a novel oral administration form for pyridin-2-ylmethylsulfinyl-1H-benzimidazoles.

Prior art

Pyridin-2-ylmethylsulfinyl-1H-benzimidazoles and compounds structurally related to these, such as are disclosed, for example, in EP-A-0005129, EP-A-0166287, EP-A-0174726, EP-A-0268956, DE-A-3531487 and EP-A-0434999, have, on account of their H^+/K^+ATPase-inhibiting action, considerable importance in the therapy of diseases which are due to increased gastric acid secretion. Examples of active compounds from this group which are commercially available or in an advanced stage of clinical testing are 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: omeprazole), 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (prop. INN: esomeprazole), 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl-sulfinyl]-1H-benzimidazole (INN: lansoprazole), 2-{[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methyl-sulfinyl}-1H-benzimidazole (INN: rabeprazole), 2-[2-(N-isobutyl-N-methylamino)benzylsulfinyl]benzimidazole (leminoprazole) and 2-(4-methoxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ylsulfinyl)-1H-benzimidazole (nepaprazole).

A common characteristic of the abovementioned pyridin-2-ylmethylsulfinyl-1H-benzimidazoles is the acid sensitivity - which is finally indispensable for their efficacy - of these active compounds, which is seen in their strong tendency to decompose in a neutral and, in particular, acidic environment, strongly colored decomposition products being formed.

In the past, there have been considerable efforts, despite the acid sensitivity of the pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, to obtain stable and storable oral administration forms which contain these compounds. There have likewise been efforts to obtain custom administration forms for pyridin-2-ylmethylsulfinyl-1H-benzimidazoles for certain application purposes.

European Patent EP-B1-244 380 claims an oral administration form for certain pyridin-2-ylmethylsulfinyl-1H-benzimidazoles in which the active compound present in the tablet or pellet core is protected from the gastric acid by an enteric coating, a water-soluble intermediate layer which is intended to protect the core and acidic coating from one another additionally being situated between the active compound core and enteric coating.

The protection of the pyridin-2-ylmethylsulfinyl-1H-benzimidazoles from gastric acid by application of an enteric coating can be regarded as the method of choice up to now when oral administration forms for this class of active compound are involved. The enteric coatings, whose resistance to gastric juice is based on the fact that free acidic groups (in particular carboxyl groups) are present in a polymer, must be separated, however, from the acid-sensitive active compound cores by suitable measures. This is carried out by application or production of a protective intermediate layer composed in whatever way (see, for example, EP-B1-589 981, WO-A-9601624, WO-A-9623500, WO-A-9624338, WO-A-9402140, WO-A-9712580 and WO-A-9800115).

Description of the invention

Surprisingly, it has now been found that an enteric coating for pyridin-2-ylmethylsulfinyl-1H-benzimidazoles is unnecessary if the coating used instead of it is designed so that the active compound is released only after a defined time, namely after gastric passage. Furthermore, it has surprisingly been found that, with a suitable design of the core comprising the active compound, the release of the active compound - once it has commenced - takes place within a short space of time, so that a rapidly rising and high active compound blood level is achieved.

The invention thus relates to an oral administration form for pyridin-2-ylmethylsulfinyl-1H-benzimidazoles and their salts, which comprises the active compound together with tablet disintegrants and is provided with a film coating which is customary per se for sustained-release compositions.

Possible oral administration forms are, for example, pellets, microtablets, minitablets or in particular tablets, if desired dispensed in capsules.

Suitable pyridin-2-ylmethylsulfinyl-1H-benzimidazoles within the meaning of the invention are, for example, omeprazole, esomeprazole, lansoprazole, rabeprazole, leminoprazole, nepaprazole and in particular pantoprazole.

Salts of the pyridin-2-ylmethylsulfinyl-1H-benzimidazoles which may be mentioned primarily are the salts with bases, in particular the sodium, potassium, calcium and magnesium salt. The pantoprazole sodium salts, in particular the pantoprazole sodium sesquihydrate, is particularly preferred.

Possible tablet disintegrants are the customary agents known to the person skilled in the art. Examples which may be mentioned are certain cellulose derivatives (e.g. sodium cellulose glycolate and Tyloses), starch, compositions based on sodium carboxymethylcellulose and potato starch (e.g. Primojel), sodium carboxymethylstarch (e.g. Explotab), bentonite, sodium alginate or pectin, but in particular chemically indifferent agents such as crosslinked polyvinylpyrrolidone (e.g. Crospovidone). The content of tablet disintegrant is customarily between 2 and 10 % by weight based on the entire core. Depending

on the type of tablet disintegrant, however, larger contents can also be used, in the case of Crospovidone, for example, 20-35% by weight.

In addition to the tablet disintegrant, if desired the tablet cores contain further auxiliaries and fillers or binders. Auxiliaries used are, in particular, lubricants and release agents. Mention may be made here, for example, of calcium salts of higher fatty acids, such as, for example, calcium stearate. Binders which may be mentioned are, in particular, polyvinylpyrrolidone and/or hydroxypropylmethylcellulose and, if desired, mannitol, which is additionally preferred as a filler.

To increase the stability of the tablet cores, it has proven advantageous to employ the pyridin-2-ylmethylsulfinyl-1H-benzimidazoles in the form of their salts and/or with addition of one or more physiologically tolerable inorganic compounds having a basic reaction. Mention may be made here, for example, of the pharmacologically tolerable alkali metal, alkaline earth metal or earth metal salts of weak acids and the pharmacologically tolerable hydroxides and oxides of alkaline earth metals and earth metals. A base to be emphasized by way of example which may be mentioned is sodium carbonate.

Film coatings customary for sustained-release compositions which may be mentioned are membranes made of plastics having a low swelling power in water, in which small soluble particles are embedded, or in particular those swellable plastic membranes which contain a small proportion of a suitable salt which determines the permeability of the film coating.

Plastics suitable for the construction of the membranes are those which are water-insoluble and physiologically tolerable. Plastics having a low swelling power in water are understood for the purposes of the present invention as meaning, for example, those which absorb not more than 5% by weight of water in aqueous medium. For this, cellulose ethers and cellulose esters are regarded as particularly suitable. In addition, suitable plastics are also polymers such as polyvinyl chloride. Swellable plastics which may be mentioned are, in particular, copolymers of acrylic and methacrylic acid esters.

Small soluble particles which may be mentioned are, for example, lactose crystals, which are preferably employed in micronized form. The particle size is expediently less than 20 µm, preferably less than 10 µm. The ratio of plastic to soluble particles can be varied within wide limits. A weight ratio of plastic to soluble particles of approximately 2:1 to 1:3 is preferred. A weight ratio of 4:3 to 4:5 is particularly preferred.

Salts suitable for the swellable plastic membranes which may be mentioned are, for example, ammonium salts, in particular quaternary ammonium salts. In a particular embodiment of plastic membranes, some of the ester groups of a copolymer of acrylic and methacrylic acid esters are ester groups having quaternary ammonium structures. An example of such copolymers having quaternary ammonium

groups which may be mentioned is trimethylammonium methyl methacrylate chloride (e.g. Eudragit RL or Eudragit RS from Röhm).

The release time of the pyridin-2-ylmethylsulfinyl-1H-benzimidazoles can be controlled within a wide range by variation of the composition of the membrane and/or by variation of the layer thickness of the membrane. Thus, release is effected at an earlier time by lowering the layer thickness of the membrane, by increasing the proportion of soluble particles, by use of the soluble particles in a more coarse-grained form or, in the case of the swellable plastic membranes, by increasing the proportion of a suitable salt (e.g. higher proportion of quaternary ammonium groups in the copolymer of acrylic and methacrylic acid esters).

The application of the membrane to the tablet cores is carried out in a manner known per se, in particular by one of the customary spraying techniques. For this, a solution of the plastic or plastic mixture intended for the membrane is prepared in a solvent or in a solvent mixture or preferably an aqueous dispersion of the plastic or plastic mixture. The soluble, micronized particles are suspended in the solution before the spraying. If necessary, the suspension is stirred during the spraying in order to prevent settling of the suspended particles. In the case of the preferred procedure using aqueous dispersions, the salts responsible for the permeability of the plastic are already contained in the plastic itself in the form of quaternary ammonium groups. In the case of application of the membrane from an aqueous dispersion, it is also possible to work under alkaline conditions.

The membrane can contain the customary auxiliaries, such as plasticizers, wetting agents, colorants and antiadherents. Pharmacologically tolerable plasticizers such as, for example, polyethylene glycols, paraffins, glycerol or propylene glycol are suitable. Wetting agents may be necessary if the coating is to be dyed with dye lakes. Sorbitol fatty acid esters or salts of dioctylsulfosuccinic acid, for example, are suitable. Antiadherents which may be mentioned are, in particular, calcium stearate or talc.

With respect to the preparation and construction of the tablet cores reference is made, for example, to the embodiments in European Patent EP-B1-589 981.

The following examples of administration forms according to the invention explain the invention in greater detail without restricting it.

Examples

Example 1: Tablets

A. Tablet cores with 10 mg of active compound

	Ingredients	per core
(a)	pantoprazole Na × 1.5 H_2O	11.28 mg
(b)	sodium carbonate, anhydrous	2.50 mg
(c)	mannitol	10.68 mg
(d)	PVP, insoluble (Crospovidone)	12.50 mg
(e)	PVP 90	1.00 mg
(f)	calcium stearate	0.80 mg
Total per core		38.75 mg

(a) is mixed with some of (b), (c) and (d). The remainder of (b) and (c) is added to the clear aqueous solution of (e) and adjusted to a pH of > 10 using (b). Granulation is carried out in a fluidized bed granulator using this solution. The remainder of (d) and (f) is added to the dried granules and the granules are pressed in a suitable tablet machine.

B. Coating

	Ingredients	Initial weight	Coating per core
(g)	Eudragit RS 30 D	2400.00 g	4.876 mg
(h)	purified water	4800.00 g	
(i)	propylene glycol	144.00 g	0.975 mg
(j)	Ca stearate	21.60 g	0.146 mg
(k)	1 N NaOH	81.10 g	0.002 mg
Total film coating		7446.70 g	6.000 mg

The ingredients are stirred to give a dispersion which is screened before processing. The dispersion is sprayed onto the cores obtained under A in a suitable apparatus.

The coating application of 6 mg per tablet core leads to a spontaneously commencing and complete release of active compound after 2 hours.

Example 2: Combinations

The following combinations of tablets according to the invention (prepared according to Example 1, comprising 10 mg of active compound, below "tablet E") and the known enteric tablets (prepared according to EP-B-589981, comprising 10 mg of active compound, below "tablet M") are, for example, conceivable, the tablets being dispensed into hard gelatin capsules of size 3:

1 tablet E + 1 tablet M
2 tablets E + 2 tablets M
3 tablets E + 1 tablet M
1 tablet E + 3 tablets M

Instead of the enteric tablets, the pellets prepared according to EP-B-589981 can also be used.

Commercial applicability

The oral administration forms according to the invention can be employed for the treatment and prevention of all the diseases which are considered to be treatable or avoidable by the use of pyridin-2-ylmethylsulfinyl-1H-benzimidazoles. In particular, the oral administration forms according to the invention can be employed in the treatment of disorders of the stomach.

Surprisingly, sustained (i.e. more or less constant over a relatively long period) release behavior is not achieved using the oral administration forms according to the invention - despite the use of a customary sustained-release coating. On the contrary, initially no active compound at all is released over a certain period, the length of this period - as explained above - being controllable by the type and thickness of the membrane.

After expiry of the adjustable period, all of the active compound is then released within a very short space of time. Due to the dissolution of the particles embedded in the membrane, the membrane becomes porous or, due to the swelling of the permeable membrane, this becomes permeable and water penetrates into the core; as a result of this the tablet disintegrant begins to swell, and when the swelling pressure is sufficient in order to disintegrate the membrane, the active compound is released spontaneously and completely.

With the aid of the oral administration form according to the invention, it is thus possible to simulate an administration of active compound at a later time. As a result, the possibility is opened up of allowing a once daily administration instead of a twice daily administration of the active compound to begin by combining, for example, in one and the same administration form (e.g. in a capsule) two active compound forms whose release is different (e.g. a customary, enteric tablet and a tablet according to the invention).

The invention therefore further relates to the combination of an oral administration form according to the invention with a conventional (i.e. enteric-coated) administration form for pyridin-2-ylmethylsulfinyl-1H-benzimidazoles. "Combination" in this connection is understood as meaning the fixed or free combination.

In the fixed combination, both administration forms are present in a single dose unit (e.g. in a common tablet of outer conventional construction and inner core coated according to the invention, in a capsule comprising conventionally coated pellets and pellets according to the invention, or in particular in a capsule comprising two or more tablets, of which at least one corresponds to the specification according to the invention).

In the free combination, the two administration forms (that according to the invention and the conventional one) are present in separate dose units, which can be contained in a common packaging unit or in separate packaging units. In a common packaging unit, the different administration forms, for example, can be arranged in the form of capsules or tablets in rows lying next to one another in a blister pack. At the time indicated by the physician, the patient would in each case successively take a capsule or tablet from each row within a short length of time (in particular within 5 minutes).

Independently of whether a fixed or free combination is present, the compliance in the case of the combination according to the invention is in any case considerably greater than when two conventional administration forms have to be taken in a relatively large space of time (for example in the space of 3 to 12 hours).

The two-fold administration of active compound simulated by the fixed or free combination leads in a relatively large space of time (compared with the same dose of active compound as a single administration) to a smaller width of variation in the active compound blood levels in the patients and moreover to more rapid symptom relief.

In this connection, the fixed combination is preferred, particularly the combination of pellets according to the invention and conventional pellets and very particularly the combination of tablets according to the invention and conventional tablets in one capsule.

The treatment dose for an adult patient is, with respect to the pyridin-2-ylmethylsulfinyl-1H-benzimidazoles or their pharmaceutically tolerable salts, approximately 5 mg to 100 mg, in particular 10 mg to 80 mg, preferably 20 mg to 40 mg per day, calculated on the free acid. This treatment dose can be evenly or unevenly divided over the two administration forms in the combination according to the invention. A more or less equal division is preferred, e.g. 20 mg of the administration form according to the invention and 20 mg of the conventional (enteric-coated) administration form, in each case based on the free acid.

For their part, the oral administration forms according to the invention or the combinations according to the invention can in turn be combined with other medicaments, in particular with antimicrobial agents, such as are employed for the control of the bacterium Helicobacter pylori (H. pylori). Suitable antimicrobial agents for the control of the bacterium H. pylori which may be mentioned are bismuth salts [e.g. bismuth subcitrate, bismuth subsalicylate, ammonium bismuth(III) potassium citrate dihydroxide, bismuth nitrate oxide, dibismuth tris(tetraoxodialuminate)], but in particular ß-lactam antibiotics, for example penicillins (such as benzylpenicillin, phenoxymethylpenicillin, propicillin, azidocillin, dicloxacillin, flucloxacillin, oxacillin, amoxycillin, bacampicillin, ampicillin, mezlocillin, piperacillin or azlocillin), cephalosporins (such as cefadroxil, cefaclor, cefalexin, cefixime, cefuroxime, cefatamet, cefadroxil, ceftibuten, cefpodoxime, cefotetan, cefazolin, cefoperazone, ceftizoxime, cefotaxime, ceftazidime,

cefamandol, cefepime, cefoxitin, cefodizime, cefsulodin, ceftriaxone, cefotiam or cefmenoxime) or other ß-lactam antibiotics (e.g. aztreonam, loracarbef or meropenem); enzyme inhibitors, for example sulbactam; tetracyclines, for example tetracycline, oxytetracycline, minocycline or doxycycline; aminoglycosides, for example tobramycin, gentamicin, neomycin, streptomycin, amikacin, netilmicin, paromomycin or spectinomycin; amphenicols, for example chloramphenicol or thiamphenicol; lincomycins and macrolide antibiotics, for example clindamycin, lincomycin, erythromycin, clarithromycin, spiramycin, roxithromycin or azithromycin; polypeptide antibiotics, for example colistin, polymixin B, teicoplanin or vancomycin; gyrase inhibitors, for example norfloxacin, cinoxacin, ciprofloxacin, pipemidic acid, enoxacin, nalidixic acid, pefloxacin, fleroxacin or ofloxacin; nitroimidazoles, for example metronidazole; or other antibiotics, for example fosfomycin or fusidic acid, where these antibacterially active substances - together with the oral administration forms according to the invention or with the combinations according to the invention - can be administered on their own or alternatively combined with one another. Combinations of antibacterially active substances which may be mentioned are, for example, amoxicillin plus metronidazole, clarithromycin plus metronidazole and amoxicillin plus clarithromycin.

Patent claims

1. An oral administration form for pyridin-2-ylmethylsulfinyl-1H-benzimidazole and its salts, which comprises the active compound together with tablet disintegrants and is provided with a film coating-customary per se for sustained which is release compositions.

2. The administration form as claimed in claim 1, wherein the pyridin-2-ylmethylsulfinyl-1H-benzimidazole is omeprazole, esomeprazole, lansoprazole, rabeprazole, leminoprazole or nepaprazole.

3. The administration form as claimed in claim 1, wherein the pyridin-2-ylmethylsulfinyl-1H-benzimidazole is pantoprazole.

4. The administration form as claimed in claim 1, wherein the tablet disintegrant is Crospovidone.

5. The administration form as claimed in claim 1, wherein the tablet disintegrant is Crospovidone having a proportion in the tablet core of 20-35% by weight.

6. The administration form as claimed in claim 1, wherein the film coating is a copolymer of acrylic and methacrylic acid esters having quaternary ammonium structures.

7. A combination consisting of an administration form as claimed in claim 1 and an administration form of a pyridin-2-ylmethylsulfinyl-1H-benzimidazole having an enteric coating.

8. The administration form as claimed in claim 1 in combination with or for combined use with an antimicrobial agent.

9. The combination as claimed in claim 7 in combination with or for combined use with an antimicrobial agent.

10. The use of administration forms and combinations as claimed in one of claims 1 to 9 in the treatment of disorders of the stomach.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/05724

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/28 A61K31/44 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y, L	WO 97 02020 A (BYK GULDEN LOMBERG CHEM FAB) 23 January 1997 (1997-01-23) the whole document	1-10
Y	WO 97 25979 A (PERIO PROD LTD) 24 July 1997 (1997-07-24) the whole document	1,6,10
Y	EP 0 519 365 A (BYK GULDEN LOMBERG CHEM FAB) 23 December 1992 (1992-12-23) cited in the application the whole document	1-10
Y	EP 0 793 959 A (TAKEDA CHEMICAL INDUSTRIES LTD) 10 September 1997 (1997-09-10) the whole document	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 October 1999	05/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fischer, W

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 42 19 390 A (BYK GULDEN LOMBERG CHEM FAB) 24 December 1992 (1992-12-24) the whole document	1-5,10
A	EP 0 526 862 A (VECTORPHARMA INT) 10 February 1993 (1993-02-10)	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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		CA 2109697 A	23-12-1992
		CN 1067809 A,B	13-01-1993
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		DE 59207438 D	28-11-1996
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		JP 6508118 T	14-09-1994
		LV 11982 A	20-03-1998
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		MX 9202961 A	01-02-1993
		NO 934648 A	16-12-1993
		NZ 243147 A	21-12-1995
		PL 169951 B	30-09-1996
		RU 2089180 C	10-09-1997
		SK 128793 A	08-06-1994
		ZW 9392 A	17-02-1993
EP 0793959 A	10-09-1997	CA 2199345 A	07-09-1997
		CN 1164424 A	12-11-1997
		JP 9295933 A	18-11-1997
DE 4219390 A	24-12-1992	AT 144416 T	15-11-1996
		AU 683411 B	13-11-1997
		AU 1974692 A	12-01-1993
		BG 61796 B	30-06-1998
		BG 98286 A	15-08-1994
		CA 2109697 A	23-12-1992
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		CZ 9302764 A	13-07-1994
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		DK 589981 T	17-03-1997
		WO 9222284 A	23-12-1992

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/05724

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4219390 A		EP 0519365 A	23-12-1992
		EP 0589981 A	06-04-1994
		ES 2096080 T	01-03-1997
		FI 935677 A	16-12-1993
		GR 3022154 T	31-03-1997
		HK 1005851 A	29-01-1999
		HR 920162 A	31-08-1996
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		NO 934648 A	16-12-1993
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		RU 2089180 C	10-09-1997
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EP 0526862 A	10-02-1993	IT 1251153 B	04-05-1995
		AT 134134 T	15-02-1996
		DE 69208299 D	28-03-1996
		DE 69208299 T	18-07-1996
		ES 2086029 T	16-06-1996

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. PCT/EP 99/05724

International Filing Date (07.08.1999) 07 AUG 1999

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* EB665WO0

Box No. I TITLE OF INVENTION

Novel oral administration form for pyridin-2-ylmethylsulfinyl-1H-benzimidazoles

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Byk Gulden
Lomberg Chemische Fabrik GmbH
Byk-Gulden-Straße 2
D-78467 Konstanz
Germany

☐ This person is also inventor.

Telephone No.
07531/84-53200

Facsimile No.
07531/84-53221

Teleprinter No.

State *(that is, country)* of nationality:
DE

State *(that is, country)* of residence:
DE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

DIETRICH, Rango
Im Tiergarten 16
D-78465 Konstanz
Germany

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:
DE

State *(that is, country)* of residence:
DE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☐ agent ☒ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Byk Gulden
Lomberg Chemische Fabrik GmbH
Byk-Gulden-Straße 2
D-78467 Konstanz
Germany

Telephone No.
07531/84-53220

Facsimile No.
07531/84-53221

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

NEY, Hartmut
Peter-Thumb-Str. 46
D-78464 Konstanz
Germany

This person is:
- [ ] applicant only
- [x] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: DE

State *(that is, country)* of residence: DE

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [x] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must st be marked)*:

Regional Patent

- ☐ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierrara Leone, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhsustan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which i is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY CCyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contractingg State of the European Patent Convention and of the PCT
- ☐ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind d of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ AE United Arab Emirates
- ☒ AL Albania .....
- ☐ AM Armenia .....
- ☐ AT Austria .....
- ☒ AU Australia .....
- ☐ AZ Azerbaijan
- ☒ BA Bosnia and Herzegovina .....
- ☐ BB Barbados
- ☒ BG Bulgaria .....
- ☒ BR Brazil .....
- ☐ BY Belarus .....
- ☒ CA Canada
- ☐ CH and LI Switzerland and Liechtenstein
- ☒ CN China .....
- ☐ CU Cuba .....
- ☒ CZ Czech Republic .....
- ☐ DE Germany .....
- ☐ DK Denmark .....
- ☒ EE Estonia .....
- ☐ ES Spain .....
- ☐ FI Finland .....
- ☐ GB United Kingdom
- ☐ GD Grenada
- ☒ GE Georgia .....
- ☐ GH Ghana .....
- ☐ GM Gambia
- ☒ HR Croatia .....
- ☒ HU Hungary .....
- ☒ ID Indonesia
- ☒ IL Israel .....
- ☒ IN India .....
- ☐ IS Iceland
- ☒ JP Japan .....
- ☐ KE Kenya .....
- ☐ KG Kyrgyzstan .....
- ☐ KP Democratic People's Republic of Korea .....
- ☒ KR Republic of Korea .....
- ☐ KZ Kazakhstan .....
- ☐ LC Saint Lucia
- ☐ LK Sri Lanka
- ☐ LR Liberia
- ☐ LS Lesotho .....
- ☒ LT Lithuania
- ☐ LU Luxembourg
- ☒ LV Latvia
- ☐ MD Republic of Moldova .....
- ☐ MG Madagascar .....
- ☒ MK The former Yugoslav Republic c of Macedonia .....
- ☐ MN Mongolia
- ☐ MW Malawi .....
- ☒ MX Mexico .....
- ☒ NO Norway
- ☒ NZ New Zealand .....
- ☒ PL Poland .....
- ☐ PT Portugal .....
- ☒ RO Romania
- ☐ RU Russian Federation .....
- ☐ SD Sudan
- ☐ SE Sweden
- ☒ SG Singapore
- ☒ SI Slovenia .....
- ☒ SK Slovakia .....
- ☐ SL Sierra Leone .....
- ☐ TJ Tajikistan .....
- ☐ TM Turkmenistan .....
- ☒ TR Turkey .....
- ☐ TT Trinidad and Tobago .....
- ☒ UA Ukraine .....
- ☐ UG Uganda .....
- ☒ US United States of America .....
- ☐ UZ Uzbekistan .....
- ☒ VN Viet Nam .....
- ☒ YU Yugoslavia .....
- ☒ ZA South Africa .....
- ☒ ZW Zimbabwe .....

Check-boxes reserved for designating States which have become party to the PCT after issuance of tthis sheet:

- ☐ CR Costa Rica .....
- ☐ DM Dominica .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes unnder Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplementalal Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to conrfirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as witithdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

PCT/EP 99 / 05724

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) (12.08.1998) 12. August 1998	98115141.8		EP	
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s):

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*: ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*

Date (day/month/year)	Number	Country (or regional Office)
18.01.1999	EP 98115141	EP

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request	:	4
description (excluding sequence listing part)	:	9
claims	:	1
abstract	:	1
drawings	:	
sequence listing part of description	:	
Total number of sheets	:	15

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☒ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Byk Gulden
Lomberg Chemische Fabrik GmbH

i.V. Dr. Herbert Rupp	i.V. Dr. Ulrich Wolf	Date	Dr. Rango Dietrich	Date	Hartmut Ney
				2.8.99	

For receiving Office use only

1. Date of actual receipt of the purported international application: 07 AUG 1999 (07. 08. 99)
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

So: LD✓ SR✓ UW:

WO 00/09092✓
PCT/EP99/05724

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:
BYK GULDEN LOMBERG CHEEMISCHE FABRIK GMBH
Byk-Gulden-Strasse 2
D-78467 Konstanz
ALLEMAGNE

EINGANG
RECEIVED
06. März 2000
Geewerblicher Reechtsschutz

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year)	
24 February 2000 (24.02.00)	
Applicant's or agent's file reference	**IMPORTANT NOTTICE**
B665WOØ	

International application No.	International filing date (day/month/year)	Priority date (day/r/month/year)
PCT/EP99/05724	07 August 1999 (07.08.99)	12 August 11998 (12.08.98)

Applicant
BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the ininternational application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,EP,IL,JP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusiIve evidence that the communication of the international application has duly taken place on the date of mailing indicateed above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,BA,BG,BR,CA,CZ,EA,EE,GE,HR,HU,ID,IN,LT,LV,MK,MX,NO,NZ,PL,RO,SG,SI,SK,TR,UA, VN,YU,ZA,ZW

   The communication will be made to those Offices only upon their request. Furthermore, those Offices ddo not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   24 February 2000 (24.02.00) under No. WO 00/09092

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by CChapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1)))

If the applicant wishes to proceed with the international application in the national phase, he must, withthin 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elelected Office.

For further important information on the time limits and acts to be performed for entering the national p phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's s Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

BYK, Gulden
Lomberg Chemische Fabrik GmbH
Byk-Gulden-Strasse 2
D-78467 Konstanz
ALLEMAGNE

Date of mailing (day/month/year) 05 October 1999 (05.10.99)	
Applicant's or agent's file reference B665WOØ	**IMPORTANT NOTIFICATION**
International application No. PCT/EP99/05724	International filing date (day/month/year) 07 August 1999 (07.08.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 12 August 1998 (12.08.98)
Applicant BYK, Gulden et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
12 Augu 1998 (12.08.98)	98115141.8	EP	23 Sept 1999 (23.09.99)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Catherine Massetti

Telephone No. (41-22) 338.83.38

15

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
B665WO0		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/05724	07/08/1999	12/08/1998
International Patent Classification (IPC) or national classification and IPC A61K9/28		
Applicant BYK GULDEN... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/02/2000	09.06.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rauter, A Telephone No. +49 89 2399 8645

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/05724

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-9	as originally filed				

Claims, No.:

1-10	as received on	14/08/1999	with letter of	13/08/1999	

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 10.

because:

☒ the said international application, or the said claims Nos. 10 with respect to industrial aplicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1 - 10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1 - 10
Industrial applicability (IA)	Yes:	Claims	1 - 9
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION III .....

1. Claim 10 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claim (Article 34(4)(a)(i) PCT).

   For the assessment of such a claim on the question whether its subject-matter is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION V. .....

1. Reference is made to the following documents:

   D1: WO-A-9 702 020
   D2: EP-A-0 519 365
   D3: EP-A-0 793 959
   D4: DE-A-4 219 390
   D5: WO-A-9 725 979

2. The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1 - 10 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

   Presently claimed administration form comprises according to independent claim 1 the essential components, ie
   - a pyridin-2-ylmethylsulfinyl-1H-benzimidazole,
   - disintegrants and
   - a film coating for sustained-release of the product.

According to claim 10 the product is used for the treatment of disorders of the stomach.

Such subject-matters can **eg** be taken from document D1 (see eg page 7, line 18 - page 9, line 4 from the bottom; claims 1, 7 and 13; and in particular, examples 3 or 4). Accordingly, the product comprises pantoprazole, disintegrants (see eg page 8, line 35 - page 9, line 1) and a sustained release coating and is used for the treatment of stomach disorders.

Further pertinent prior art which takes away novelty:
D2: See eg page 2, line 39 - page 3, line 12; examples;
D3: See eg column 1, line 57 - column 2, line 13; column 4, lines 29 and 30; column 4, line 43 - column 6, line 15; column 5, line 52; examples;
D4: See eg claims 1 and 2; column 2, lines 33 - 59.

Dependent claims 2 - 9 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty as the specific embodiments are comprised by the disclosure of the cited prior art. With regard to the specified pyridin-2-ylmethylsulfinyl-1H-benzimidazoles see eg D3, PVP as disintegrant, antimicrobial agents and enteric coatings are used in eg D1.

SECTION VII. .....

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D3 - D5 is not mentioned in the description, nor are these documents identified therein.

SECTION VIII. .....

1. The claims comprise product names which probably represent registered trade marks which have not been identified as such.

Patent claims

1. An oral administration form for pyridin-2-ylmethylsulfinyl-1H-benzimidazole and its salts, which comprises the active compound together with tablet disintegrants and is provided with a film coating which is customary per se for sustained-release compositions.

2. The administration form as claimed in claim 1, wherein the pyridin-2-ylmethylsulfinyl-1H-benzimidazole is omeprazole, esomeprazole, lansoprazole, rabeprazole, leminoprazole or nepaprazole.

3. The administration form as claimed in claim 1, wherein the pyridin-2-ylmethylsulfinyl-1H-benzimidazole is pantoprazole.

4. The administration form as claimed in claim 1, wherein the tablet disintegrant is Crospovidone.

5. The administration form as claimed in claim 1, wherein the tablet disintegrant is Crospovidone having a proportion in the tablet core of 20-35% by weight.

6. The administration form as claimed in claim 1, wherein the film coating is a copolymer of acrylic and methacrylic acid esters having quaternary ammonium structures.

7. A combination consisting of an administration form as claimed in claim 1 and an administration form of a pyridin-2-ylmethylsulfinyl-1H-benzimidazole having an enteric coating.

8. The administration form as claimed in claim 1 in combination with or for combined use with an antimicrobial agent.

9. The combination as claimed in claim 7 in combination with or for combined use with an antimicrobial agent.

10. The use of administration forms and combinations as claimed in one of claims 1 to 9 in the treatment of disorders of the stomach.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
B665W00		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/05724	07/08/1999	12/08/1998
Applicant		
BYK, Gulden et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   ORAL ADMINISTRATION FORM FOR PYRIDIN-2-YLMETHYLSULFINYL-1H-BENZIMIDAZOLES

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/05724

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/28 A61K31/44 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y, L	WO 97 02020 A (BYK GULDEN LOMBERG CHEM FAB) 23 January 1997 (1997-01-23) the whole document ---	1-10
Y	WO 97 25979 A (PERIO PROD LTD) 24 July 1997 (1997-07-24) the whole document ---	1,6,10
Y	EP 0 519 365 A (BYK GULDEN LOMBERG CHEM FAB) 23 December 1992 (1992-12-23) cited in the application the whole document ---	1-10
Y	EP 0 793 959 A (TAKEDA CHEMICAL INDUSTRIES LTD) 10 September 1997 (1997-09-10) the whole document --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 October 1999	05/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Fischer, W

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/05724

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 42 19 390 A (BYK GULDEN LOMBERG CHEM FAB) 24 December 1992 (1992-12-24) the whole document	1-5,10
A	EP 0 526 862 A (VECTORPHARMA INT) 10 February 1993 (1993-02-10)	

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/05724

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9702020 A	23-01-1997	US 5945124 A	31-08-1999
		AU 6517496 A	05-02-1997
		CA 2232450 A	23-01-1997
		EP 0841903 A	20-05-1998
		JP 11508577 T	27-07-1999
WO 9725979 A	24-07-1997	US 5840332 A	24-11-1998
		AU 1206597 A	11-08-1997
		CN 1208343 A	17-02-1999
		CZ 9802198 A	16-12-1998
		EP 0877604 A	18-11-1998
EP 0519365 A	23-12-1992	AT 144416 T	15-11-1996
		AU 683411 B	13-11-1997
		AU 1974692 A	12-01-1993
		BG 61796 B	30-06-1998
		BG 98286 A	15-08-1994
		CA 2109697 A	23-12-1992
		CN 1067809 A,B	13-01-1993
		CZ 9302764 A	13-07-1994
		DE 4219390 A	24-12-1992
		DE 59207438 D	28-11-1996
		DK 589981 T	17-03-1997
		WO 9222284 A	23-12-1992
		EP 0589981 A	06-04-1994
		ES 2096080 T	01-03-1997
		FI 935677 A	16-12-1993
		GR 3022154 T	31-03-1997
		HK 1005851 A	29-01-1999
		HR 920162 A	31-08-1996
		IE 77640 B	31-12-1997
		IL 102096 A	18-06-1996
		JP 6508118 T	14-09-1994
		LV 11982 A	20-03-1998
		LV 11982 B	20-09-1998
		MX 9202961 A	01-02-1993
		NO 934648 A	16-12-1993
		NZ 243147 A	21-12-1995
		PL 169951 B	30-09-1996
		RU 2089180 C	10-09-1997
		SK 128793 A	08-06-1994
		ZW 9392 A	17-02-1993
EP 0793959 A	10-09-1997	CA 2199345 A	07-09-1997
		CN 1164424 A	12-11-1997
		JP 9295933 A	18-11-1997
DE 4219390 A	24-12-1992	AT 144416 T	15-11-1996
		AU 683411 B	13-11-1997
		AU 1974692 A	12-01-1993
		BG 61796 B	30-06-1998
		BG 98286 A	15-08-1994
		CA 2109697 A	23-12-1992
		CN 1067809 A,B	13-01-1993
		CZ 9302764 A	13-07-1994
		DE 59207438 D	28-11-1996
		DK 589981 T	17-03-1997
		WO 9222284 A	23-12-1992

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/05724

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4219390 A		EP 0519365 A	23-12-1992
		EP 0589981 A	06-04-1994
		ES 2096080 T	01-03-1997
		FI 935677 A	16-12-1993
		GR 3022154 T	31-03-1997
		HK 1005851 A	29-01-1999
		HR 920162 A	31-08-1996
		IE 77640 B	31-12-1997
		IL 102096 A	18-06-1996
		JP 6508118 T	14-09-1994
		LV 11982 A	20-03-1998
		LV 11982 B	20-09-1998
		MX 9202961 A	01-02-1993
		NO 934648 A	16-12-1993
		NZ 243147 A	21-12-1995
		PL 169951 B	30-09-1996
		RU 2089180 C	10-09-1997
		SK 128793 A	08-06-1994
		ZW 9392 A	17-02-1993
EP 0526862 A	10-02-1993	IT 1251153 B	04-05-1995
		AT 134134 T	15-02-1996
		DE 69208299 D	28-03-1996
		DE 69208299 T	18-07-1996
		ES 2086029 T	16-06-1996

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
B665WO0		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/05724	07/08/1999	12/08/1998
International Patent Classification (IPC) or national classification and IPC		
A61K9/28		
Applicant		
BYK GULDEN... et al.		

1. This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/02/2000	09.06.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rauter. A Telephone No. +49 89 2399 8645

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/05724

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-9 as originally filed

Claims, No.:

1-10 as received on 14/08/1999 with letter of 13/08/1999

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial appplicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 10.

because:

- ☒ the said international application, or the said claims Nos. 10 with respect to industrial aaplicability relate to the following subject matter which does not require an international preliminary examinatioon (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that noo meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1 - 10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1 - 10
Industrial applicability (IA)	Yes:	Claims	1 - 9
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the queestion whether the claims are fully supported by the description, are made:

see separate sheet

SECTION III .....

1. Claim 10 relates to subject-matter considered by this Authority to be ccovered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be f formulated with respect to the industrial applicability of the subject-matter of thesee claim (Article 34(4)(a)(i) PCT).

   For the assessment of such a claim on the question whether its subjeect-matter is industrially applicable, no unified criteria exist in the PCT Contracting ! States. The patentability can also be dependent upon the formulation of the claimss. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, , however, claims to a known compound for first use in medical treatment and thee use of such a compound for the manufacture of a medicament for a new medical t treatment.

SECTION V. .....

1. Reference is made to the following documents:

   D1: WO-A-9 702 020
   D2: EP-A-0 519 365
   D3: EP-A-0 793 959
   D4: DE-A-4 219 390
   D5: WO-A-9 725 979

2. The present application does not satisfy the criterion set forth in Articble 33(2) PCT because the subject-matter of claims 1 - 10 is not new in respect of porior art as defined in the regulations (Rule 64(1)-(3) PCT).

   Presently claimed administration form comprises according to indepeendent claim 1 the essential components, ie
   - a pyridin-2-ylmethylsulfinyl-1H-benzimidazole,
   - disintegrants and
   - a film coating for sustained-release of the product.

According to claim 10 the product is used for the treatment of disorders of the stomach.

Such subject-matters can **eg** be taken from document D1 (see eg pagge 7, line 18 - page 9, line 4 from the bottom; claims 1, 7 and 13; and in particular, examples 3 or 4). Accordingly, the product comprises pantoprazole, disintegrants (see eg page 8, line 35 - page 9, line 1) and a sustained release coating and is used for the treatment of stomach disorders.

Further pertinent prior art which takes away novelty:
D2: See eg page 2, line 39 - page 3, line 12; examples;
D3: See eg column 1, line 57 - column 2, line 13; column 4, lines 29 aand 30; column 4, line 43 - column 6, line 15; column 5, line 52; exampless;
D4: See eg claims 1 and 2; column 2, lines 33 - 59.

Dependent claims 2 - 9 do not contain any features which, in combinaation with the features of any claim to which they refer, meet the requirements of thee PCT in respect of novelty as the specific embodiments are comprised by the disclosure of the cited prior art. With regard to the specified pyridin-2-ylmethylsulfinyl-1H-benzimidazoles see eg D3, PVP as disintegrant, antimicrobial agents and enteric coatings are used in eg D1.

SECTION VII. .....

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant backkground art disclosed in the documents D1, D3 - D5 is not mentioned in the descrription, nor are these documents identified therein.

SECTION VIII. .....

1. The claims comprise product names which probably represent registered trade marks which have not been identified as such.

Patent claims

1. An oral administration form for pyridin-2-ylmethylsulfinyl-1H-benzimidazole and its salts, which comprises the active compound together with tablet disintegrants and is provided with a film coating-customary per se for sustained which is release compositions.

2. The administration form as claimed in claim 1, wherein the pyridin-2-ylmethylsulfinyl-1H-benzimidazole is omeprazole, esomeprazole, lansoprazole, rabeprazole, leminoprazole or nepaprazole.

3. The administration form as claimed in claim 1, wherein the pyridin-2-ylmethylsulfinyl-1H-benzimidazole is pantoprazole.

4. The administration form as claimed in claim 1, wherein the tablet disintegrant is Crospovidone.

5. The administration form as claimed in claim 1, wherein the tablet disintegrant is Crospovidone having a proportion in the tablet core of 20-35% by weight.

6. The administration form as claimed in claim 1, wherein the film coating is a copolymer of acrylic and methacrylic acid esters having quaternary ammonium structures.

7. A combination consisting of an administration form as claimed in claim 1 and an administration form of a pyridin-2-ylmethylsulfinyl-1H-benzimidazole having an enteric coating.

8. The administration form as claimed in claim 1 in combination with or for combined use with an antimicrobial agent.

9. The combination as claimed in claim 7 in combination with or for combined use with an antimicrobial agent.

10. The use of administration forms and combinations as claimed in one of claims 1 to 9 in the treatment of disorders of the stomach.